Factors associated with prolonged viral RNA shedding in patients with COVID-19

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Summary

In this retrospective study of 113 patients, we were able to identify independent risk factors of prolonged viral RNA shedding in COVID-19 patients, specifically: male sex, delayed admission to hospital after illness onset, and invasive mechanical ventilation.

Abstract

Background. An outbreak of coronavirus disease 2019 (COVID-19) is becoming a public health emergency. Data are limited on the duration and host factors related to viral shedding.

Methods. In this retrospective study, risk factors associated with severe acute respiratory coronavirus 2 (SARS-CoV-2) RNA shedding were evaluated in a cohort of 113 symptomatic patients from two hospitals outside Wuhan.

Results. The median duration of SARS-CoV-2 RNA detection was 17 days (Interquartile Range [IQR], 13–22 days) as measured from illness onset. When comparing patients with early (<15 days) and late viral RNA clearance (≥15 days after illness onset), prolonged SARS-CoV-2 RNA shedding was associated with male sex (p=0.009), old age (p=0.033), concomitated with hypertension (p=0.009), delayed admission to hospital after illness onset (p=0.001), severe illness at admission (p=0.049), invasive mechanical ventilation (p=0.006), and corticosteroid treatment (p=0.025). Patients with longer SARS-CoV-2 RNA shedding duration had slower recovery of body temperature (p<0.001) and focal absorption on radiograph images (p<0.001) than patients with early SARS-CoV-2 RNA clearance. Male sex (odds ratio [OR], 3.24 [95% CI, 1.31–8.02]), delayed hospital admission (OR, 1.30 [95% CI, 1.10–1.54]), and invasive mechanical ventilation (OR, 9.88 [95% CI, 1.11–88.02]) were independent risk factors for prolonged SARS-CoV-2 RNA shedding.

Conclusions. Male sex, delayed admission to hospital after illness onset, and invasive mechanical ventilation were associated with prolonged SARS-CoV-2 RNA shedding. Hospital admission and general treatments should be started as soon as possible in symptomatic COVID-19 patients, especially male patients.

Key words

Coronavirus, viral shedding, risk factors, SARS-COV-2, COVID-19

Abbreviation:

Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Acute respiratory distress syndrome (ARDS), Interquartile range (IQR), Odds ratio (OR), Real-time reverse transcription–polymerase chain reaction (RT-PCR), Cycle threshold value (Ct-value), Confidence interval (CI), Middle East Respiratory Syndrome (MERS)

Introduction

The outbreak of severe acute respiratory coronavirus 2 (SARS-CoV-2) induced pneumonia is becoming a public health emergency [1]. As of Mar 20, 2020, more than 260,000 confirmed infections have been reported worldwide, with over 11,000 deaths [2]. Several studies have summarized the clinical and epidemiological features of patients with coronavirus disease 2019 (COVID-19). Knowledge was accumulating about the clinical course and outcomes of critically ill patients with COVID-19, while information about patients with mild severity is scarce. Compared with the severity of patients in Wuhan, those patients outside Wuhan displayed more relatively mild symptoms [3]. According to the report with the largest sample size so far, 80.9% of the 44,672 patients displayed symptoms considered mild [4]. The data on the clinical course, particularly on viral RNA shedding of mild COVID-19 patients, is of paramount importance to optimize treatment options and prevent transmission of this disease.

One of the release criteria for hospitalized patients with mild symptoms is a sputum/oral swab testing negative twice in a 24-h interval [5]. The viral RNA excretion pattern in respiratory specimens during the process of SARS-CoV-2 infection has been analyzed in limited studies. Zou et al. studied the viral load in sequential nasal and throat swabs in patients with COVID-19 [6]. Higher viral loads were detected soon after symptom onset, while symptomatic and asymptomatic patients had similar viral load [6]. It was suggested that the viral nucleic acid shedding pattern of patients with COVID-19 resembles that of patients with influenza and appears different from that seen in patients infected with SARS-CoV-1 [7, 8]. The pattern of SARS-CoV-2 RNA shedding during the course of treatment has not been well characterized. Zhang et al. found that after 5 days of therapy, only 25% patients showed oral swabs negative [9]. However, in this research, little clinical information was involved and not correlated with virological data.

Here, we did a retrospective study to elucidate trends in clinical illness and viral RNA shedding associated with COVID-19, and to identify risk factors influencing the persistence of SARS-CoV-2 RNA shedding. Our results suggest that male patients, delayed admission to hospital after illness onset, and invasive mechanical ventilation during hospitalization were associated with prolonged SARS-CoV-2 RNA shedding. These results reinforce guidance that hospital admission and general treatments should be started as soon as possible in symptomatic patients with COVID-19. Male patients need particular attention for their prolonged viral RNA shedding, which might be associated with poor treatment outcomes.

Methods

Study design and Participants

A total of 113 patients with confirmed SARS-CoV-2 infection admitted to the First Affiliated Hospital, School of Medicine, Zhejiang University and the Shenzhen Third People's Hospital were enrolled (**Figure 1**). The earliest patient in Shenzhen center was admitted on January 13th, 2020. And the first patient in Hangzhou center was admitted on January 19th, 2020. As of Feb 19, a total of 161 confirmed patients were admitted to the two hospitals. Since COVID-19 is an emerging acute infectious disease, the primary purpose of this study was to evaluate the occurrence of viral RNA clearance in the first 21 days after illness onset. Patients were enrolled if they met one of the three inclusion criteria: 1. disease duration over 21 days without viral RNA clearance; 2. viral RNA clearance occurred within 21 days; 3. death occurred within 21 days. According to the criteria, 47 patients were excluded as they were less than 21 days since illness onset and without viral RNA clearance. And one patient was excluded, as she was transferred to the local hospital without viral RNA clearance (**Figure 1**). In the cohort of 113 patients, sixty-nine patients were cured and released

in 21 days; thirteen patients were still hospitalized over 21 days but had viral RNA clearance within 21 days; twenty-nine patients had viral RNA detectable over 21 days; and two patients died with viral RNA clearance within 21 days (**Figure 1**). Ethics approval was obtained from the Institutional Review Board of the First Affiliated Hospital, School of Medicine, Zhejiang University.

The diagnosis and severity of illness at admission were assessed based on the latest guidelines of SARS-CoV-2 infection enacted by WHO on March 13, 2020 [10]. As described, patients could be categorized into five levels of severity: mild illness, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), and sepsis or septic shock. To simplify the analysis process, mild illness and pneumonia cases were combined as “mild cases”, and severe pneumonia, ARDS, and sepsis or septic shock cases were combined as “severe cases” in this study. All the patients in this study were symptomatic patients. Most of the mild cases were patients with pneumonia except for two cases had no radiological manifestation. Critically severe illness was defined as occurrence of ARDS, sepsis, or septic shock.

Clinical characteristics, treatments and outcome data were obtained from electronic medical records. The following results associated with treatment processes were recorded: (i) temperature recovery, indicated by a patient’s ear temperature decreasing to no higher than 37.5°C and not increasing thereafter. (ii) Radiological recovery was defined as improvement of initial pulmonary lesions without appearance of new radiological lesions at other sites. (iii) Duration of viral RNA shedding was considered the number of days from symptom onset to persistent negative detection of respiratory tract specimens. All subsequent samples from the same patients were then tested until three consecutive samples were negative with the first negative sample defining the duration

of shedding. (iv) Whether invasive mechanical ventilation was performed during hospitalization. (v) Duration of hospitalization.

Virological Investigations

SARS-CoV-2 infection was confirmed in all patients by testing respiratory specimens with a real-time reverse transcription–polymerase chain reaction (RT-PCR) assay (Shanghai Bio-germ Medical Technology Co Ltd). Specimens of the respiratory tract such as sputum, nasopharyngeal swab or throat swab samples were collected daily. Since all the patients in this study were hospitalized patients, lower respiratory tract specimens such as sputum, endotracheal aspirate, or bronchoalveolar lavage fluid were preferred over nasopharyngeal or throat swab. The proportion of nasopharyngeal or throat swab samples taken was lower than 10% of all samples. We performed the specimen collection process according to the manufacturer's protocol. Diagnosis followed the criteria recommended by the National Institute for Viral Disease Control and Prevention (China) (http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html). A cycle threshold value (Ct-value) less than 37 was defined as a positive test result, while a Ct-value of 40 or more was defined as a negative. Specimens with a Ct-value of 37 to 40 required confirmation by retesting.

Statistical Analysis

Continuous variables were expressed as median with inter quartile range (IQR) and were compared by Kruskal-Wallis test. Categorical variables were expressed as number (%) and compared by Chi-square (χ^2) test or Fisher's exact test (if more than 20% of the cells had an expected count of less than 5). Significant risk factors identified on univariate analyses were further analyzed by multiple logistic regressions to identify independent risk factors associated with the prolonged duration of SARS-CoV-2 shedding. We used Kaplan-Meier survival analysis to estimate the cumulative SARS-CoV-

2 RNA–negativity rate and the stratified log-rank statistic to compare the difference of SARS-CoV-2 clearance between different groups. All statistical analyses were performed using the SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). The significance level of the hypothesis tests was set at 0.05 (two-sided).

Results

Clinical characteristics of patients in this study

The study population included 113 symptomatic patients with confirmed SARS-CoV-2 infection. Clinical characteristics of these patients are summarized in Table 1. Among 113 patients, the median age was 52 years, and 58.4% were male. The epidemiological data showed that 62.8% had exposure history to Hubei province, and 40.7% patients had exposure history to confirmed patients. The median time from illness onset to hospital admission was 5 days (IQR, 3–8 days). Common underlying concomitant diseases included hypertension (26 cases), diabetes (9 cases), and coronary heart disease (6 cases) (**supplementary Table 1**). Among the patients, 8 patients were current smokers. Most of the patients had mild symptoms, and only 28.3% of the cohort was diagnosed as severe illness at admission. Lopinavir/ritonavir and interferon-α were the most frequently used antiviral regimens (**supplementary Table 1**). On the basis of lopinavir/ritonavir and interferon-α combination, 55 patients (48.7%) also received Umifenovir, and another 19 patients (16.8%) were treated with Ribavirin. Corticosteroid was used in 56.6% patients. The primary purpose of this study is to observe the clinical outcome of patients in the first 21 days after illness onset. There were 74.3% (84) patients that had viral RNA clearance within 21 days after illness onset (**Figure 1**). The median duration of viral shedding of these 84 patients was 15 days (IQR, 11.75–18 days). With the viral shedding duration of all the 113 patients included, the median duration of SARS-CoV-2 RNA detection from illness onset was 17 days (IQR, 13–22 days). There were 61.1% (69) patients of the

cohort that were cured and discharged in 3 weeks, with a median hospital stay of 15 days (IQR, 12-17 days). As of March 20, 2020, a total of 105 patients were cured and discharged, with a median hospital stay of 18 days (IQR, 14-27 days). Twenty-three patients met the diagnostic criteria as critically severe illness (ARDS, sepsis, or septic shock) during hospitalization, eighteen patients underwent invasive mechanical ventilation, and two deaths occurred. Ninety-one patients had fever as an initial symptom of illness. The median time from illness onset to body temperature recovery to normal was 11 days (IQR, 8-14 days). As of March 22, 2020, one hundred and six patients had signs of recovery with radiological imaging, and the median duration from illness onset to radiological recovery was 15 days (IQR, 11-18 days).

Risk factors for prolonged duration of SARS-CoV-2 RNA shedding

The primary purpose of this study is to observe the occurrence of viral RNA clearance within 21 days after illness onset. Among the 113 patients enrolled, there were 84 patients that had viral RNA clearance within 21 days. The median duration of viral RNA shedding for these 84 patients was 15 days. Patients were further divided into two groups; one group was patients that had persistent negative viral detection results < 15 days after illness onset (n=37), and another group was patients with prolonged viral RNA shedding ≥15 days after illness onset (n=79). Epidemiological and clinical characteristics, treatment therapy, and outcomes were compared between the two groups (**Table 1**). Prolonged RNA shedding was associated with males (p=0.009), old age (p=0.033), and concomitant hypertension (p=0.009). The ratio of severe patients at admission in the group with prolonged shedding was significantly higher than that in the group with early viral RNA clearance (34.2% vs. 16.2%, p=0.049). Corticosteroid (p=0.025) and invasive mechanical ventilation (p=0.006) treatments were related to prolonged viral RNA shedding time.

Prolonged RNA shedding was associated with delayed recovery on radiological image (median days, 12 vs. 16, p<0.001), delayed recovery of body temperature (median days, 7 vs. 11, p<0.001), and prolonged hospital stay (median days, 13.5 vs. 22, p<0.001). More patients were cured and released in 21 days after illness onset (91.9% vs. 46.1%, p=0.023) in the group with early viral RNA clearance than in the group with prolonged viral RNA shedding.

Variables with statistical significance (p<0.05) between early and late viral RNA clearance groups, including age, male sex, hypertension, use of corticosteroid, duration from illness onset to hospitalization, severe illness at admission, critically severe illness in hospitalization, and occurrence of mechanical ventilation, were tested in a multivariable model. Multivariate analysis indicated that the time from illness onset to hospital admission (OR, 1.30 [95% CI, 1.10–1.54], p=0.002), and male patients (OR, 3.24 [95% CI, 1.31–8.02], p=0.011) were independent factors associated with the duration of SARS-CoV-2 RNA shedding (**Table 2**). From the Kaplan-Meier curves, the cumulative probability of viral negative conversion was slightly higher in the female group than that in male group (p=0.043, **Figure 2A**). Kaplan-Meier curve analysis showed that patients admitted to the hospital 5 days after illness onset achieved a higher probability of faster viral RNA clearance (p=0.021; **Figure 2B**) than those patients admitted to hospital over 5 days after illness onset. SARS-CoV-2 RNA clearance was significantly delayed in patients who had invasive mechanical ventilation during hospitalization (OR, 9.88 [95% CI, 1.11–88.02], p=0.04) compared with those without invasive mechanical ventilation (**Table 2, Figure 2C**).

Disease progression related to sex and hospital admission time

Among the 113 patients, 41.6% (47 patients) were female, and 58.4% (66 patients) were male. Illness severity at admission and treatment outcomes were compared between male and female

patients (**Table 3**). The median duration of SARS-CoV-2 RNA shedding was 15 days (IQR, 12–17 days) in the female group and 18.5 days (IQR, 15–25 days) in the male group (p=0.013). The ratio of severe patients at admission in the male group (37.9%) was significantly higher than that in the female group (14.9%, p=0.010). The median length of hospital stay was longer in the male group than in the female group (median days, 15 vs. 22, p=0.002). Early (≤5 days) versus later (>5 days) hospital admission was significantly associated with viral RNA clearance speed (p=0.004). Late hospital admission was associated with a higher ratio of severe patients at admission (43.4% vs. 15.0%, p=0.001), and higher frequency of critically severe illness in hospitalization (30.2% vs. 11.7%, p=0.019) than early hospital admission (**Table 3**).

Discussion

Studies on COVID-19 have generally been limited to the description of the initial clinical, hematological, and radiological findings. So far, there has been little investigation of the duration of SARS-CoV-2 RNA shedding. This study is the first to document the risk factors associated with prolonged SARS-CoV-2 shedding in the respiratory tract among a cohort of COVID-19 patients. We found that the median duration from onset of symptoms to RNA clearance was 17 days. Male sex, delayed hospital admission, and invasive mechanical ventilation were independent risk factors for prolonged SARS-CoV-2 RNA shedding.

Male patients usually had more severe symptoms at admission and longer viral RNA shedding than female patients with COVID-19. This observation may indicate that males are more severely affected than females by the SARS-CoV-2 infection. Studies from the SARS and Middle East Respiratory Syndrome (MERS) epidemic already indicated that there may be sex-related differences in disease outcomes [11, 12]. The findings here are consistent with a recent epidemiological report including

44,672 confirmed cases in China, which showed the case fatality rate was 2.8% for males and 1.7% for females [4]. It was suggested that sex-related difference was confounded by other variables such as comorbidity conditions or smoking history. The smoking rates were comparable between early clearance group and prolonged shedding group in this study. There was higher percentage of patients with hypertension in prolonged viral RNA shedding group than in early clearance group. But hypertension was not a significant risk factor in the logistic regression model. Thus, it was suggested that sex itself is the influencing factor of disease progression.

The specific mechanism of sex-related difference in SARS-CoV-2 infection is unclear. Women as a population are thought to be more immune-privileged than males, as they exhibit lower infection and mortality rates with infectious diseases, and display higher responses to various types of vaccination than men [13]. The specific mechanism may be related to sex hormones, which could modulate immunocompetence [14]. Sex-specific immune responses have been found to contribute to enhanced susceptibility of male mice to SARS-CoV-1 infection [19]. We propose that another one of the potential mechanisms might be related to human angiotensin-converting enzyme 2 (ACE2) expression. ACE2 is a functional receptor for SARS-CoV-1 [15]. SARS-CoV-2 has been confirmed to use this same cell entry receptor as SARS-CoV-1 [16]. Results of animal studies demonstrated that tissue-specific regulation of ACE2 by sex hormones could contribute to sex-related differences in obesity-hypertension [17]. The modulation and angiotensin II level by ACE2 and ACE could partly explain the sex-specific susceptibility to diabetes and diabetic nephropathy [18]. Further in-depth mechanical studies are warranted to understand the sex-related dimorphism of COVID-19.

Our findings also suggest that symptomatic patients should be admitted to hospital as early as possible if SARS-CoV-2 infection is confirmed. Delayed hospital admission was associated with more

severe conditions at admission and worse treatment outcomes. There have been no specific antiviral drugs for SARS-CoV-2. In our study, lopinavir/ritonavir and interferon-α were the most frequently used antiviral regimens. It was hard to evaluate the efficacy of these two-drug combination because of the lack of the controls. However, the association between early admission to hospital and early viral RNA clearance might indicate a potential effect of these treatments [20, 21]. Recently, a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection showed no benefit of lopinavir–ritonavir treatment beyond standard care [22]. The efficacy of lopinavir/ritonavir and interferon-α in combination should be evaluated in clinical trials. General supportive treatment might also help to accelerate the process of recovery.

Several observational studies have reported that corticosteroid therapy was linked to persistent viral RNA shedding in patients with avian influenza A (H7N9), MERS, and SARS [23-25]. Corticosteroid usage was related to prolonged viral RNA shedding time in this report was well, as patients with early RNA clearance had lower ratio of patients using corticosteroid than patients with late RNA clearance (40.5% vs. 64.5%, P=0.025). However, this difference can be influenced by disease severity, as patients who were given corticosteroid usually were more severe than those were not. Further, corticosteroid was not found to be an independent risk factor of prolonged viral RNA shedding in the multivariable model conducted in this report. Thus, a definitive conclusion that corticosteroid treatment is associated with prolonged viral RNA shedding duration in patients with COVID-19 cannot be drawn. The reason of inconsistent results might be the corticosteroid dosing in this report was relatively low (0.5-1 mg methylprednisolone/kg body weight) for COVID-19 patients.

Invasive mechanical ventilator support was found to be another important independent predictor of prolonged viral RNA shedding. There were several reasons for the delayed viral RNA clearance in

patients with invasive mechanical ventilator support. One was that the detection rate of coronavirus RNA differed among various types of respiratory tract specimens. Highly pathogenic avian influenza A(H5N1) virus RNA can be detected longer and at higher levels in lower respiratory tract specimens than in upper respiratory tract specimens [26]. For viruses that replicate primarily in lower respiratory tract tissue, endotracheal aspirate specimens from patients who receive invasive mechanical ventilation usually have higher and sustained viral RNA shedding than specimens in upper respiratory tract tissue [27-29]. Kinetic analysis of viral RNA shedding in MERS patients showed that viral secretion in the lower respiratory tract was more sustained in patients who suffered from more severe pneumonia than mild patients [30]. Another potential reason for prolonged duration of viral RNA shedding is the emergence of drug resistance during antiviral treatment, since most of the patients with invasive mechanical ventilation had a longer hospital stay.

This study had some limitations. One was that although viral RNA was detected in most of the studies, the viral RNA shedding is not exactly the same as viral shedding. So far, it is not known how shedding of viral RNA correlates with shedding of infectious virus. Second, the standard treatment included antiviral treatment with lopinavir/ritonavir, interferon-α, and general supportive treatment. Since nearly all the patients were given this standard treatment, we were not able to judge if these treatments had effect on viral RNA shedding. Third, for patients with invasive mechanical ventilation, lower respiratory tract specimens were collected. Bias might be introduced when comparing differences directly in viral RNA shedding between sputum versus endotracheal aspirate or bronchoalveolar lavage fluid.

In conclusion, prolonged SARS-CoV-2 RNA shedding in the respiratory tract was independently associated with delayed admission to hospital, male sex, and invasive mechanical ventilation. These

results reinforce guidance that hospital admission and treatments should be started as soon as possible in patients with COVID-19. Male patients need particular attention for their prolonged viral RNA shedding, which might be associated with poor treatment outcomes. Understanding the virological dynamics during the process of illness should be helpful in the clinical management of patients with COVID-19.

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Declaration of interests

We declare no competing interests.

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Table 1. Comparison of clinical characteristics and treatment responses between groups with different shedding duration

	All patients (N=113)		Viral shedding duration after illness onset				p^*
			N	<15 days (N=37)	N	≥ 15 days (N=76)	
Age, y	113	52 (43, 63)	37	48 (34, 61)	76	54.5 (45, 63)	0.033
Male sex	113	58.4%（66）	37	40.5% (15)	76	67.1% (51)	0.009
Exposure history in Hubei	113	62.8% (71)	37	67.6% (25)	76	60.5% (46)	0.467
Exposure history to confirmed patients	113	40.7% (46)	37	51.4% (19)	76	35.5% (27)	0.108
Duration from illness onset to hospital admission, d	113	5 (3, 8)	37	4 (2, 6)	76	6 (4, 9)	0.001
Severe patients at admission	113	28.3% (32)	37	16.2% (6)	76	34.2% (26)	0.049
Comorbidity							
Hypertension	113	23.0% (26)	37	8.1% (3)	76	30.3% (23)	0.009
Diabetes	113	8.0% (9)	37	5.4% (2)	76	9.2% (7)	0.715
Coronary heart disease	113	5.3% (6)	37	5.4% (2)	76	5.3% (4)	1
Current smoker	113	7.1% (8)	37	8.1% (3)	76	6.6% (5)	0.715
Treatment							
Corticosteroid	113	56.6% (64)	37	40.5% (15)	76	64.5% (49)	0.025
Umifenovir	113	48.7% (55)	37	43.2% (16)	76	51.3% (39)	0.420
Ribavirin	113	16.8% (19)	37	8.1% (3)	76	21.1% (16)	0.084

Invasive mechanical ventilation	113	15.9% (18)	37	2.7% (1)	76	22.4% (17)	0.006
Outcome							
Duration of viral RNA shedding, d[#]	113	17 (13, 22)	37	11 (8, 13)	76	20 (16.5, 25.5)	<0.001
Duration from illness onset to radiologic recovery, d[#]	106	15 (11, 18)	37	12 (10, 15)	69	16 (13, 21)	<0.001
Duration from illness onset to temperature recovery, d[#]	91	11 (8, 14)	29	7 (6, 11)	62	11 (10, 14)	<0.001
Days of hospitalization, d[#]	105	18 (14, 27)	36	13.5 (11.5, 17)	69	22 (16, 30)	<0.001
Critical illness in hospitalization	113	20.4% (23)	37	5.4% (2)	76	27.6% (21)	0.006
Cured in 21 days	113	61.1% (69)	37	91.9% (34)	76	46.1% (35)	0.023
In-hospital mortality in 21 days	113	1.8% (2)	37	0.0% (0)	76	2.6% (2)	1

*, Chi-square (χ^2) test or Fisher's exact test was used with $P < 0.05$ as significant. #, hospitalization data as of March 20, 2020.

The occurrence data are shown as no. (%) unless otherwise indicated. Values indicate no. of positive results/total no. of patients with available assay results.

The time data are shown as median data and inter quartile range data in brackets.

Table 2. Multivariable analyses of factors associated with duration of SARS-CoV-2 Virus RNA detection

Variable	Multivariable analysis			Stepwise analysis		
	Odds ratio (OR)	95% CI	p	Odds ratio (OR)	95% CI	p
Age	1.00	0.96-1.03	0.913			
Male sex	2.89	1.10-7.58	0.031	3.24	1.31-8.02	0.011
Hypertension	3.94	0.86-18.15	0.079			
Corticosteroid	1.38	0.52-3.65	0.519			
Time from illness onset to hospitalization, d	1.31	1.08-.158	0.005	1.30	1.10-1.54	0.002
Severe patients at admission	1.10	0.32-3.81	0.882			
Critical illness in hospitalization	0.42	0.03-5.22	0.497			
Invasive mechanical ventilation	23.28	0.72-750.09	0.076	9.88	1.11-88.02	0.04

Table 3. Comparison of treatment outcomes between groups of different sex or duration time from illness onset to hospital admission

	Duration from illness onset to hospital admission			Sex		
	≤5 days (n=60)	>5 days (n=53)	*P**	Female (n=47)	Male (n=66)	*P**
Severe patients at admission	15.0% (9)	43.4% (23)	0.001	14.9% (7)	37.9% (25)	0.010
Duration of viral shedding, d#	15 (10, 20)	19 (15, 25)	0.004	15 (12, 17)	18.5 (15, 25)	0.013
Duration from illness onset to radiologic recovery, d#	15 (10, 18)	15 (13, 20)	0.201	15 (12, 17)	16 (11, 20)	0.567
Duration from illness onset to temperature recovery, d#	10 (7, 13)	11 (9, 15)	0.058	10 (7, 12)	11 (8, 15)	0.114
Cured in 21 days	58.3% (35)	64.2% (34)	0.2216	72.3% (34)	53.0% (35)	0.152
Invasive mechanical ventilation	11.7% (7)	20.8% (11)	0.188	10.6% (5)	19.7% (13)	0.195
Critical illness in hospitalization	11.7% (7)	30.2% (16)	0.019	12.8% (6)	25.8% (17)	0.091
Days of hospitalization, d	21 (14, 29.5)	17 (14, 23)	0.095	15 (12, 20)	22 (16, 29.5)	0.002
In-hospital mortality	0.0% (0)	3.8% (2)	0.218	0.0% (0)	3.0% (2)	0.51

*, Chi-square (χ^2) test or Fisher's exact test was used with $P < 0.05$ as significant. #, hospitalization data as of March 20, 2020.

The occurrence data are shown as no. (%) unless otherwise indicated. Values indicate no. of positive results/total no. of patients with available assay results.

The time data are shown as median data and inter quartile range data in brackets.

Figure legends

Figure 1. Flow diagram of patients with confirmed COVID-19 included in this study and their clinical outcomes at 21 days after illness onset.

Figure 2. A. Cumulative proportion of patients with detectable SARS-CoV-2 RNA by day after illness onset between male patients and female patients (log-rank P = 0.043). **B**. Cumulative proportion of patients with detectable SARS-CoV-2 RNA by day after illness onset between patients admitted to the hospital ≤ 5 days and those admitted > 5 days after illness onset (log-rank P = 0.021). **C.** Cumulative proportion of patients with detectable SARS-CoV-2 RNA by day after illness onset between patients who had invasive mechanical ventilation and those who did not (log-rank P < 0.001).

Figure1

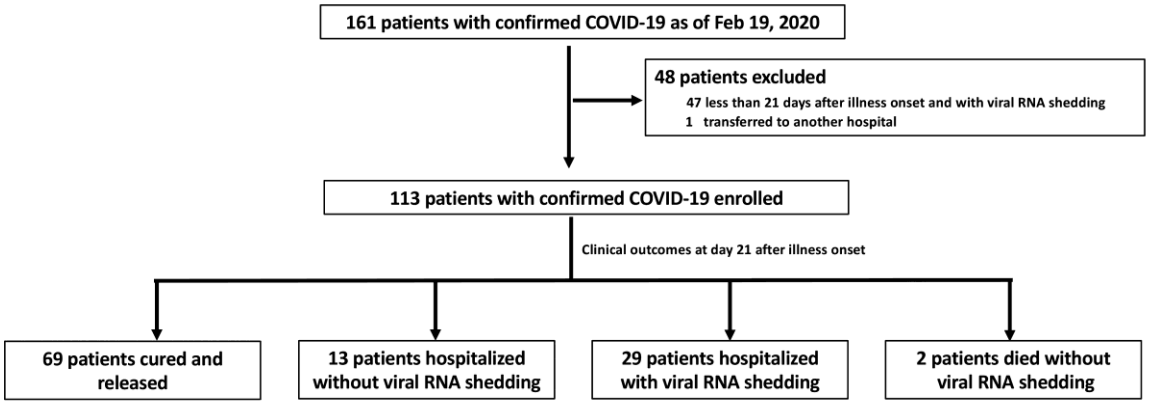
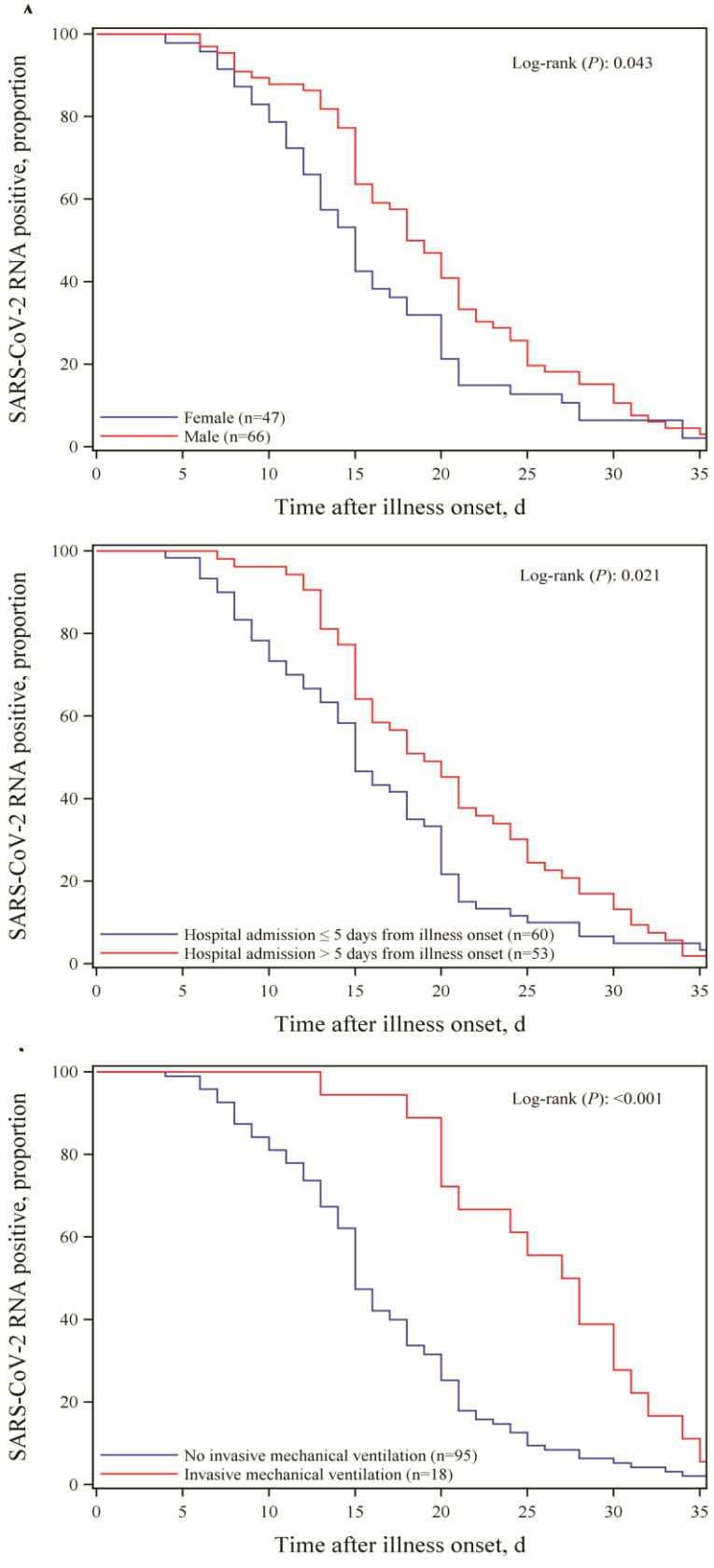


Figure 2


A
SARS-CoV-2 RNA positive, proportion
Log-rank (P): 0.043
Female (n=47)
Male (n=66)
Time after illness onset, d
SARS-CoV-2 RNA positive, proportion
Log-rank (P): 0.021
Hospital admission ≤ 5 days from illness onset (n=60)
Hospital admission > 5 days from illness onset (n=53)
Time after illness onset, d
SARS-CoV-2 RNA positive, proportion
Log-rank (P): <0.001
No invasive mechanical ventilation (n=95)
Invasive mechanical ventilation (n=18)
Time after illness onset, d